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EXAMINER	
EMCH, GREGORY S	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/084,380	CHAIN, DANIEL G.	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14,19,20,25,55,56,72,75 and 93-116* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14,19,20,25,55,56,72,75 and 93-116* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/24/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 117-120 have been canceled as requested in the amendment filed on 24 July 2009.

Claims 14, 19, 20, 25, 55, 56, 72, 75 and 93-116 are under examination in the instant office action.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 24 July 2009 was filed after the mailing date of the non-final Office action on 27 May 2009. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Withdrawn Objections/Rejections

It is acknowledged that duplicate claims 117-120 have been canceled.

The rejection of claims 117-120 under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (EP 0 613 007) and further in view of Mak et al. (Brain Res. 1994 Dec 19;667(1):138-42) is withdrawn as moot in response to the cancellation of said claims.

Remaining issues are set forth below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (EP 0 613 007, published 31 August 1994; Citation N on PTO-892 dated 27 May 2009) and further in view of Audia et al. (US 5,965,614; issued 12 October 1999; effective priority date of 22 November 1996; Citation A on PTO-892 dated 27 May 2009).

Becker et al. teach the use of conformationally-specific antibodies and antibody fragments which bind to amyloid β (Aβ) peptides for the treatment of amyloid accumulation diseases, such as Alzheimer's disease. Some of these antibodies bind selectively with those Aβ peptides, which are predominantly in a β-sheet conformation and some of the antibodies bind to Aβ peptides, which have adopted a random coil or α-helix conformation (col.5, lines 42-50; col.7, lines 49-52). Becker teaches that such antibodies would be useful in inhibiting the neurotoxicity associated with the

accumulation of oligomeric Aβ in Alzheimer's disease (col.1, lines 1-18; col.5, lines 27-41). Becker teaches antibodies that bind to dissociated (i.e., soluble Aβ, including Aβ 1-40) and those that bind to aggregated Aβ, wherein administration of both types of antibodies is therapeutically effective in treating the neurotoxicity associated with Alzheimer's disease (col.2, lines 38-50; col.5, lines 42-50; col.7, lines 49-52), as in claims 14 and 20. Becker teaches monoclonal antibodies, humanized antibodies, chimeric antibodies, antibody binding fragments (including Fab, $F(ab')_2$ and Fv fragments) and single-chain antibodies (col.5, line 50 – col.6, line 12), as in claims 19, 25, 55, 56, 93-98 and 105-108. It is noted that the active method steps of independent claims 14, 20 and 105 are essentially the same, i.e. said claims require contacting an Aβ peptide with an exogenous free-end specific antibody in the cerebrospinal fluid (CSF) of an Alzheimer's patient. The contacting steps in these claims are taught by Becker, since Becker teaches administration of the antibodies for therapeutic treatment of Alzheimer's disease patients, which would necessarily reach the cerebrospinal fluid of the patients (see e.g. col.8, lines 16-42). That is, the active step recited in the claims is administering (in general) and does not require administration to the CSF. The claims are construed to encompass any route of administration, and since Becker teaches that the method is sufficient to treat Alzheimer's, the antibodies must reach the CSF. It is noted that the instant specification (see paragraphs [0010], [0043], and [0090]) indicates that the methods can include routes of administration other than directly to the CSF. Since the antibodies would necessarily reach the CSF and bind the Aβ peptide therein, Becker inherently teaches a method of obtaining an amyloid β-peptide-antibody

complex which comprises forming a composition consisting essentially of: an Aβ antibody, cerebrospinal fluid and said Aβ peptide, as in claims 93-98.

Becker does not explicitly teach contacting *in vivo* soluble Aβ in the cerebrospinal fluid of an Alzheimer's patient with an exogenous free-end specific antibody which is targeted to a free N-terminus or a free C-terminus of Aβ 1-40. However, Audia teaches that the Aβ monoclonal antibody 3D6 binds specifically to residues 1-5 of Aβ and that said antibody does not recognize secreted amyloid precursor protein (APP) or full-length APP, but detects Aβ species with an amino terminal aspartic acid, i.e. at position 1 of Aβ peptide (col.49, lines 21-24), as in claims 55, 56, 93-98 and 105-108. Audia's antibody is "free-end specific" as instantly claimed, since it does not bind to APP (see description at e.g. p.8, lines 10-17 of the specification). Audia does not teach administration of the free end specific antibody for inhibiting accumulation and neurotoxicity associated with Alzheimer's disease.

However, it would have been *prima facie* obvious to the artisan of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the disclosures of Becker and Audia. The skilled artisan would have been motivated to use the 3D6 antibody, i.e. which is a free-end specific antibody directed to the N-terminus of Aβ, in Becker's therapeutic methods because Audia teaches that said antibody is highly specific for Aβ and does not cross react with other closely related molecules, such as APP. That is, since Becker teaches that administration of any Aβ antibody would be useful to treat Alzheimer's disease and Audia teaches that the 3D6 antibody specifically targets the art-recognized peptide involved in the neuropathology

of said disease, it would be obvious to use Audia's antibody in Becker's therapeutic methods. Thus, the skilled artisan would have had a reasonable expectation of success that the 3D6 antibody would be successful in treating the neurotoxicity associated with Alzheimer's disease, since it specifically targets Aβ, which is associated with the neurotoxicity in Alzheimer's disease.

In the reply filed on 24 July 2009, applicant asserts that Becker, taken as a whole, indicates that anti-Aβ antibodies that are specific for Aβ in the β-sheet conformation might be used in diagnostic and therapeutic methods. Applicant asserts that Becker contains no suggestion that any other antibodies might be useful as therapeutic agents. Applicant asserts that to the extent Becker discloses anti-Aβ antibodies specific for Aβ in an α-helix or random coil conformation, one of ordinary skill in the art would understand that such antibodies might be used as a reagent in assays for an agent that inhibit the neurotoxicity of β-amyloid peptide (see claims 3 and 5). Applicant asserts that upon reading Becker, one of ordinary skill in the art would understand that such antibodies would not be suitable as Alzheimer's disease therapeutics, because Becker states explicitly that there is "minimal neurotoxicity" associated with the Aβ conformation that is recognized by the antibodies. Applicant asserts that his stance is consistent with the state of the art at the time the instant application was filed as evidenced by Soto et al., which discloses that Aβ peptides exist as either "amyloidogenic conformers" and "non-amyloidogenic conformers." Applicant asserts that Soto performs experiments to determine the fibrillogenic potential of different Aβ peptides and conformers and concludes that the α-helix or random coil

conformation is poorly amyloidogenic and sensitive to proteolysis. Thus, applicant asserts that both Becker and Soto make it clear that antibodies that recognize soluble Aβ having a predominantly random coil conformation would not be useful as a therapeutic antibody. Applicant asserts that the sections in Becker quoted by the examiner in the previous office action do not support that Becker teaches that any antibody to Aβ would be useful for treating Alzheimer's disease. Applicant asserts that Becker teaches away from the claimed invention and that Audia does not cure Becker's deficiencies. Applicant asserts that Audia provides no rationale for using the 3D6 antibody in methods of treating Alzheimer's disease, as Audia mentions 3D6 only in the context of a β-amyloid sandwich assay. Applicant asserts that the examiner used the instant specification to arrive at the motivation to combine the prior art to arrive at the claimed invention. Applicant asserts that the Examiner fails to point to any evidence that before the filing of the instant application one of ordinary skill in the art would have had any reason to believe it was desirable to use an antibody that recognized the Aβ peptide, but did not recognize APP, for treating Alzheimer's disease. Applicant asserts that the examiner did not provide any support for his conclusion that it would have been obvious to use a monoclonal antibody that binds to Aβ that is soluble in the CSF.

Applicant's arguments have been fully considered and are not found persuasive. Although Becker teaches that Aβ in the β-sheet conformation is the predominant neurotoxic species, this does not teach away from using anti-Aβ antibodies that are specific for Aβ that is predominantly in an α-helix or random coil conformation for treatment. Becker states at col.7, lines 26-52:

> Some of the antibodies of the present invention demonstrate specificity for beta -amyloid peptides which are predominantly beta-sheet in conformation, as predominantly is defined supra. These antibodies show little binding specificity for beta-amyloid peptides which have a great deal of random coil and/or α-helix in the secondary structure.
> In another embodiment of this invention are antibodies which are specific for beta-amyloid peptides which have adopted a random coil or alpha -helix conformation. These antibodies show little binding specificity for beta-amyloid peptides which have a great deal of beta -sheet conformation.
> These antibodies are used in diagnostics, therapeutics or in diagnostic/therapeutic combinations. By "diagnostics" as used herein is meant testing that is related to either the in vitro or in vivo diagnosis of disease states or biological status in mammals, preferably in humans. By "therapeutics" and "therapeutic/diagnostic combinations" as used herein is respectively meant the treatment or the diagnosis and treatment of disease states or biological status via the in vivo administration to mammals, preferably humans, of the antibodies of the present invention. The antibodies of the present invention are especially preferred in the diagnosis and/or treatment of Alzheimer's disease in mammals, preferably humans. (Emphasis added.)

> Becker states at col.8, lines 16-18:
>
> The antibodies of the present invention are useful in the diagnosis and treatment of mammals suffering from Alzheimer's disease.

Thus, applicant's assertion that Becker contains no suggestion that antibodies other than those specific for Aβ in the β-sheet conformation might be useful as a therapeutic agent is erroneous. Becker describes antibodies to the α-helix conformation of Aβ and in the next sentence states that "these" antibodies are used in therapeutics. This is an explicit suggestion to use the antibodies to Aβ in the α-helix or random coil conformation for treatment of Alzheimer's disease. Moreover, Becker teaches that "some of the antibodies of the present invention" bind to the β-sheet conformation, while "in another embodiment of this invention are antibodies" specific for the α-helix or random coil conformation. Becker then states that "the antibodies of the present

invention are especially preferred in the diagnosis and/or treatment of Alzheimer's disease in mammals, preferably humans." This latter statement is interpreted as a generic teaching that either of the two types of antibodies would be useful for Alzheimer's disease treatment. Only a reason, suggestion or motivation need appear in the cited prior art in order to combine references under 35 U.S.C. 103. *Pro Mold Tool Col. v. Great Lakes Plastics, Inc.,* 75 F.3d 1568, 1573, 37 USPQ2d 1626, 1629 (Fed. Cir. 1996). Given Becker's explicit suggestion to use antibodies of either conformation to Aβ (and thus "any" antibody to Aβ), it would at least be obvious for the artisan of ordinary skill to try using antibodies to the α-helix or random coil conformation for treatment, which is a proper rationale to support a finding of obviousness under 35 U.S.C. 103(a). See the Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>).

That Becker teaches that anti-Aβ antibodies specific for the β-sheet conformation of Aβ is the preferred embodiment does not mean that Becker teaches away from using anti-Aβ antibodies specific for the α-helix or random coil conformation. This is supported by MPEP §2123 (II), which states "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. *In re Susi,* 440 F.2d 442, 169 USPQ 423 (CCPA 1971). 'A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.' *In re Gurley*, 27 F.3d 551, 554, 31 USPQ2d 1130, 1132 (Fed. Cir. 1994) (The invention was directed

to an epoxy impregnated fiber-reinforced printed circuit material. The applied prior art reference taught a printed circuit material similar to that of the claims but impregnated with polyester-imide resin instead of epoxy. The reference, however, disclosed that epoxy was known for this use, but that epoxy impregnated circuit boards have 'relatively acceptable dimensional stability' and 'some degree of flexibility,' but are inferior to circuit boards impregnated with polyester-imide resins. The court upheld the rejection concluding that applicant's argument that the reference teaches away from using epoxy was insufficient to overcome the rejection since 'Gurley asserted no discovery beyond what was known in the art.' 27 F.3d at 554, 31 USPQ2d at 1132.). Furthermore, '[t]he prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed..' *In re Fulton*, 391 F.3d 1195, 1201, 73 USPQ2d 1141, 1146 (Fed. Cir. 2004). Additionally, MPEP §2123 (I) states, "A reference may be relied upon for all that it would have reasonably suggested to one having ordinary skill the art, including nonpreferred embodiments. *Merck & Co. v. Biocraft Laboratories*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied,* 493 U.S. 975 (1989). See also >*Upsher-Smith Labs. v. Pamlab, LLC*, 412 F.3d 1319, 1323, 75 USPQ2d 1213, 1215 (Fed. Cir. 2005)(reference disclosing optional inclusion of a particular component teaches compositions that both do and do not contain that component);< Celeritas Technologies Ltd. v. Rockwell International Corp., 150 F.3d 1354, 1361, 47 USPQ2d 1516, 1522-23 (Fed. Cir. 1998) (The court held that the prior art anticipated the claims even though it taught away from the claimed invention. 'The

fact that a modem with a single carrier data signal is shown to be less than optimal does not vitiate the fact that it is disclosed.)." Indeed, as set forth above, Becker describes antibodies to the α-helix conformation of Aβ and in the next sentence states that "these" antibodies are used in therapeutics. This is hardly a teaching away from treatment with antibodies to the α-helix conformation of Aβ.

Regarding applicant's assertion that one of ordinary skill in the art would understand that antibodies to the α-helix or random coil conformation might be used as a reagent in assays for agent that inhibit the neurotoxicity of β-amyloid peptide, this is again not a teaching away from using such antibodies for treatment. In considering the disclosure of a reference, it is proper to take into account not only specific teaching of the reference but also the inferences which one skilled in the art would be reasonably be expected to draw therefrom. *In re Preda*, 401 F.2d 825, 159 USPQ 342, 344 (CCPA 1968). Claim 3 of Becker is drawn to a method for assaying for agents which inhibit the neurotoxicity of β-amyloid peptide which comprises: (a) causing a sample of purified beta -amyloid peptide to adopt a predominantly non beta -sheet conformation; (b) incubating potential inhibitors of neurotoxicity with the β-amyloid peptide in non β-sheet conformation; (c) manipulating the β-amyloid peptide in such a way that β-amyloid peptide without the potential inhibitor of neurotoxicity adopts a predominantly β-sheet conformation; (d) measuring the neurotoxic properties of each beta -amyloid peptide/potential inhibitor mixture; and (e) detecting reduction in the neurotoxicity relative to a control. Claim 5 of Becker is drawn to a method as claimed in claim 3 wherein said β-amyloid peptide in predominantly non β-sheet conformation has adopted

less than 50% of its potential β-sheet conformation. Given Becker's suggestion that antibodies to either conformation would be useful for therapeutics, the artisan of ordinary skill would have known that antibodies to the α-helix conformation of Aβ could be tested in the methods of claims 3 and 5. Indeed, Becker at col.5, lines 34-41, teaches, "The use, therefore, of β-amyloid peptide which has adopted a predominantly β-sheet conformation allows the development of compounds which specifically inhibit the neurotoxicity. The neurotoxicity assays described, supra, can then be supplemented by the incubation of the β-amyloid peptide with potential inhibitors of neurotoxicity. The reduction in neurotoxicity can then be observed in an efficient manner" (Emphasis added). The next paragraph of the reference (col.5, lines 42-50) teaches, "Another embodiment of this invention encompasses conformationally-specific antibodies and antibody fragments which bind to β-amyloid peptides in a secondary structure-specific manner. Some of these antibodies bind only those β-amyloid peptides which are predominantly in a β-sheet conformation. A second set of these antibodies bind only those β-amyloid peptides which have adopted a random coil or α-helix conformation." Upon reading this information, the skilled artisan would know that the antibodies would be "potential inhibitors of neurotoxicity" and that these could be tested in the neurotoxicity assay. If the artisan then tested these antibodies in the claimed assay, the artisan would necessarily see that antibodies to the α-helix conformation would prevent neurotoxicity since the β-amyloid peptides would be prevented from forming the neurotoxic β-sheet conformation.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The examiner has relied on knowledge which was within the level of skill in the antibody arts and the knowledge of one of ordinary skill in the art the time the invention was made. Such an artisan knew and currently knows that the more specific an antibody to a particular antigen (and thus the less the antibody cross-reacts with other proteins), the more the antibody is useful for treatment of disease characterized by the pathogenic antigen. Here, Becker repeatedly associates the pathology of Alzheimer's disease with the Aβ protein itself (and not with the APP protein). Thus, it would be *prima facie* obvious to the artisan of ordinary skill in the art that an antibody, such as the 3D6 antibody taught by Audia, which is highly specific for the pathogenic protein, Aβ, and not other closely related proteins, such as APP, would be preferred for treatment of Alzheimer's disease.

Applicant's argument that there is no suggestion to combine the references is inaccurate. In the instant case, the skilled artisan would have been motivated to use the 3D6 antibody, i.e. which is a free-end specific antibody directed to the N-terminus of Aβ, in Becker's therapeutic methods because Audia teaches that said antibody is highly

specific for Aβ and does not cross react with other closely related molecules, such as APP. That is, since Becker teaches that administration of any Aβ antibody would be useful to treat Alzheimer's disease and Audia teaches that the 3D6 antibody specifically targets the art-recognized peptide involved in the neuropathology of said disease, it would be obvious to use Audia's antibody in Becker's therapeutic methods.

Claims 14, 19, 20, 25, 55, 56, 93-98 and 105-108 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (EP 0 613 007, published 31 August 1994; Citation N on PTO-892 dated 27 May 2009), further in view of Audia et al. (US 5,965,614; issued 12 October 1999; effective priority date of 22 November 1996; Citation A on PTO-892 dated 27 May 2009) and as evidenced by Johnson-Wood et al. (PNAS, Feb. 1997, citation AO on IDS dated 03 June 2002).

It is noted that the instant rejection is virtually identical to the rejection set forth above but with further motivation provided by the prior art reference by Johnson-Wood. Becker et al. teach as set forth above but do not explicitly teach contacting *in vivo* soluble Aβ in the cerebrospinal fluid of an Alzheimer's patient with an exogenous free-end specific antibody which is targeted to a free N-terminus or a free C-terminus of Aβ 1-40. However, Audia teaches that the Aβ monoclonal antibody 3D6 binds specifically to residues 1-5 of Aβ and that said antibody does not recognize secreted amyloid precursor protein (APP) or full-length APP, but detects Aβ species with an amino terminal aspartic acid, i.e. at position 1 of Aβ peptide (col.49, lines 21-24), as in claims 55, 56, 93-98 and 105-108. Audia's antibody is "free-end specific" as instantly claimed,

since it does not bind to APP (see description at e.g. p.8, lines 10-17 of the specification). Audia does not teach administration of the free end specific antibody for inhibiting accumulation and neurotoxicity associated with Alzheimer's disease.

However, it would have been *prima facie* obvious to the artisan of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the disclosures of Becker and Audia. The skilled artisan would have been motivated to use the 3D6 antibody, i.e. which is a free-end specific antibody directed to the N-terminus of Aβ, in Becker's therapeutic methods because Audia teaches that said antibody is highly specific for Aβ and does not cross react with other closely related molecules, such as APP. That is, since Becker teaches that administration of any Aβ antibody would be useful to treat Alzheimer's disease and Audia teaches that said antibody specifically targets the art-recognized peptide involved in the neuropathology of said disease, it would be obvious to use Audia's antibody in Becker's therapeutic methods. Furthermore, Johnson-Wood teaches that 3D6 is free-end specific (p. 1551, first column, section on Abeta measurement), and that it binds to amyloid plaques very well (see Figure 4 and p. 1553, paragraph spanning the 2 columns). This guides the artisan of ordinary skill to select 3D6 based on its superior ability to bind the plaques known to be associated with Alzheimer's disease. Thus, the skilled artisan would have had a reasonable expectation of success that the 3D6 antibody would be successful in treating the neurotoxicity associated with Alzheimer's disease, since it specifically targets Aβ and blinds to Aβ plaques, which are associated with the neurotoxicity in Alzheimer's disease.

In the reply filed on 24 July 2009, applicant asserts that the examiner cites Johnson-Wood for the proposition that antibody 3D6 "binds to amyloid plaques very well" and that this "guides the artisan of ordinary skill to select 3D6 based on its superior ability to bind the plaques known to be associated with Alzheimer's disease." Applicant asserts that the examiner's statement underscores the fact that it would not have been obvious to treat Alzheimer's disease with a free-end specific antibody that binds to soluble Aβ in the CSF because it was accepted that Aβ plaques were "associated with the neurotoxicity in Alzheimer's disease." Applicant notes that antibody 3D6 does in fact bind to Aβ that is soluble in CSF but that this property is inherent to 3D6 and was not appreciated in the prior art. Applicant asserts that the inherent, unappreciated property that antibody 3D6 binds to soluble Aβ is irrelevant to a rejection under section 103.

Applicant's arguments have been fully considered and are not found persuasive. The examiner agrees that the inherent, unappreciated property that antibody 3D6 binds to soluble Aβ is irrelevant to the instant rejection. The instant finding of obviousness is not based on the inherent property of 3D6 of binding to soluble Aβ as opposed to other forms of Abeta, such as aggregated. The instant finding of obviousness is only for selection of a particular antibody (in the instant case, 3D6) for treatment of Alzheimer's disease. That is, as set forth above, Audia teaches that the Aβ monoclonal antibody 3D6 binds specifically to residues 1-5 of Aβ and that said antibody does not recognize secreted amyloid precursor protein (APP) or full-length APP, but detects Aβ species with an amino terminal aspartic acid, i.e. at position 1 of Aβ peptide (col.49, lines 21-24).

This fact would motivate the artisan to use the antibody for treatment since it binds with high specificity to the pathogenic Aβ protein. Johnson-Wood provides further motivation to select 3D6 and administer it for Alzheimer's disease treatment since it teaches that 3D6 binds to amyloid plaques very well (see Figure 4 and p. 1553, paragraph spanning the 2 columns). This guides the artisan of ordinary skill to select 3D6 based on its superior ability to bind the plaques known to be associated with the pathology of Alzheimer's disease. That is, even without knowing that 3D6 antibody inherently binds to the soluble form of Aβ, one of ordinary skill in the art would have found it obvious to select this antibody for use in Becker's methods, because Johnson-Wood teaches the superior Aβ -binding qualities of this particular antibody.

Claims 14, 19, 20, 25, 72, 75, 99-104 and 109-116 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (EP 0 613 007, published 31 August 1994) and further in view of Mak et al. (Polyclonals to beta-amyloid(1-42) identify most plaque and vascular deposits in Alzheimer cortex, but not striatum. Brain Res. 1994 Dec 19;667(1):138-42).

As set forth above, Becker teaches the use of conformationally-specific antibodies and antibody fragments which bind to amyloid β (Aβ) peptides for the treatment of amyloid accumulation diseases, such as Alzheimer's disease. Some of these antibodies bind selectively with those Aβ peptides, which are predominantly in a β-sheet conformation and some of the antibodies bind to Aβ peptides, which have adopted a random coil or α-helix conformation (col.5, lines 42-50; col.7, lines 49-52).

Becker teaches that such antibodies would be useful in inhibiting the neurotoxicity associated with the accumulation of oligomeric Aβ in Alzheimer's disease (col.1, lines 1-18; col.5, lines 27-41). Becker teaches antibodies that bind to dissociated, (i.e., soluble Aβ, including Aβ 1-40) and those that bind to aggregated Aβ, wherein administration of both types of antibodies is therapeutically effective in treating the neurotoxicity associated with Alzheimer's disease (col.2, lines 38-50; col.5, lines 42-50; col.7, lines 49-52), as in claims 14 and 20. Becker teaches monoclonal antibodies, humanized antibodies, chimeric antibodies, antibody binding fragments (including Fab, $F(ab')_2$ and Fv fragments) and single-chain antibodies (col.5, line 50 – col.6, line 12), as in claims 19, 25, 99-104 and 109-120. It is noted that the active method steps of independent claims 14, 20, 109, 113 and 117 are essentially the same, i.e. said claims require contacting an Aβ peptide with an exogenous free-end specific antibody in the cerebrospinal fluid of an Alzheimer's patient. The contacting step in these claims are taught by Becker, since Becker teaches administration of the antibodies for therapeutic treatment of Alzheimer's disease patients, which would necessarily reach the cerebrospinal fluid of the patients (see e.g. col.8, lines 16-42). That is, the active step recited in the claims is administering (in general) and does not require administration to the CSF. The claims are construed to encompass any route of administration, and since Becker teaches that the method is sufficient to treat Alzheimer's, the antibodies must reach the CSF. It is noted that the instant specification (see paragraphs [0010], [0043], and [0090]) indicates that the methods can include routes of administration other than directly to the CSF. Since the antibodies would necessarily reach the CSF and

bind the Aβ peptide therein, Becker inherently teaches a method of obtaining an amyloid β-peptide-antibody complex which comprises forming a composition consisting essentially of: an Aβ antibody, cerebrospinal fluid and said Aβ peptide, as in claims 99-104.

Becker does not explicitly teach contacting *in vivo* soluble Aβ in the cerebrospinal fluid of an Alzheimer's patient with an exogenous free-end specific antibody which is targeted to a free C-terminus of Aβ 1-40, as in claims 72, 75, 99-104 and 109-120. However, Mak teaches that polyclonal antibodies which are raised to Aβ 34-40 are capable of binding to Aβ 1-40, but not to Aβ 1-42 (see p.138, abstract and second paragraph). Since the antibodies do not bind to a longer form of Aβ (Aβ 1-42), the antibodies would not bind to APP either, since APP contains Aβ 1-42. It is noted that Mak teaches that the antibody "was predominantly reactive against β40 and was specific for β40 after absorption on β42" (p. 138, 2nd paragraph). It would be obvious to the artisan to perform the same method steps for purification of the antibody and use said antibody after it has been purified (as in the cited portion of Mak's disclosure). This would result in an antibody that is more specifically targeted to the Aβ 1-40 peptide, which Mak teaches is involved in disease pathology. Mak does not teach administration of the free end specific antibody for inhibiting accumulation and neurotoxicity associated with Alzheimer's disease.

However, it would have been *prima facie* obvious to the artisan of ordinary skill in the art at the time the invention was made to arrive at the claimed invention by combining the disclosures of Becker and Mak. The skilled artisan would have been

motivated to use the antibodies to Aβ 34-40, i.e. which is a free end-specific antibody directed to the C-terminus of Aβ 1-40, in Becker's therapeutic methods. This is because Mak teaches that said antibodies are highly specific for Aβ 1-40, that this peptide is involved in the neuropathology of Alzheimer's disease, and that this peptide is the major species present in the CSF of Alzheimer's disease patients (see p.138, first paragraph). Further, Mak suggests that the C-terminus of Aβ may be an important variable in Alzheimer's disease pathology (see p.138, first paragraph). Thus, the artisan would be motivated to use antibodies to Aβ 34-40 to attempt to treat Alzheimer's disease. Moreover, given that Becker teaches monoclonal antibodies and other chimeric antibodies, it would be obvious for the artisan of ordinary skill to generate a monoclonal antibody from Mak's polyclonals. Thus, the artisan would have had a reasonable expectation of success that the antibodies to Aβ 34-40 would be successful in treating the neurotoxicity associated with Alzheimer's disease.

In the reply filed on 24 July 2009, applicant asserts that the portion of Mak cited by the examiner (page 138, first paragraph), merely states that Aβ1-40 is the major species present in CSF. Applicant asserts that Mak contains no suggestion that Aβ1-40 "is involved in the neuropathology of Alzheimer's disease." Applicant asserts that the text cited by the examiner reiterates that Aβ1-42 "tends to aggregate, is not readily cleared and accumulates in cells." Applicant asserts that this disclosure reflects the art-accepted view that neuritic plaques are the pathogenic agent in Alzheimer's disease and that the Aβ1-42 predominates in plaques and that none of the text in Mak cited by the examiner suggests that a free-end specific antibody to the free C-terminus of Aβ1-

40 could or should be used in a method to treat Alzheimer's disease by contacting the antibody with soluble Aβ in the CSF. Applicant asserts that neither Becker nor Mak, either alone or in combination, provides any rationale to substitute Mak's antibody in Becker's asserted methods for treating Alzheimer's disease. Applicant again alleges that the examiner has used hindsight reasoning from applicant's disclosure.

Applicant's arguments have been fully considered and are not found persuasive. Applicant's argument that Mak contains no suggestion that Aβ1-40 is involved in the neuropathology of Alzheimer's disease is incorrect. At p.138, first sentence, Mak states, "Deposition of a 28-43 amino acid peptide, β-protein (Aβ) accompanies Alzheimer's disease (AD)." This an explicit suggestion that Aβ 1-40 is involved in Alzheimer's disease, since it is taught to be one of the proteins (28-43 amino acids long) that are deposited in Alzheimer's disease. Again, in response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). Here, the examiner was relying only on knowledge which was within the level of ordinary skill at the time the claimed invention was made and which was taken from teachings provided by the prior art of record, i.e. Becker and Mak.

Declaration under 37 CFR 1.132

The declaration under 37 CFR 1.132 filed on 13 May 2009, i.e., the Chain declaration, is insufficient to overcome the outstanding rejections under 35 U.S.C. 103 (a).

Item (4) of the declaration states that Wyeth and Elan have taken a license under the subject application and any patent that matures from it, to develop and market the free-end specific antibodies to amyloid β for the treatment of Alzheimer's disease, including bapineuzumab, the humanized version of antibody 3D6 that is disclosed in Audia et el., U,S. Patent No. 5,965,614, which is specific for the free N- terminus of amyloid. Item (5) states that a second major pharmaceutical company has taken a license under the subject application and any patent that matures from the application, to develop and market free-end specific antibodies to amyloid β for the treatment of Alzheimer's disease. Item (6) states that Glaxo Group Limited ("OSK") has taken an option under the subject application and any patent that matures from the application, to develop and market antibodies to amyloid β for the treatment of Alzheimer's disease. The declaration states that Exhibits A-C are copies of the licensing agreements.

In applicant's Remarks submitted on 24 July 2009, applicant asserts that these licensing agreements are strong objective evidence that at the time the invention was filed, the claimed invention was not obvious. Applicant asserts that the statements (set forth in Exhibits A-C) by Wyeth and Elan (identifying the free-end specific antibody bapineuzumab as their "lead therapeutic compound" for treatment of Alzheimer's disease) and of Pfizer (stating explicitly that the free end-specificity of PF-04360365

"may be beneficial for the risk/benefit profile of this molecule") and the commencement of clinical trials with these free end-specific antibodies, rather than any other antibodies, provide evidence that treatment of Alzheimer's disease with free-end specific antibodies is highly preferred as compared to methods of treating Alzheimer's disease with other types of antibodies, such as disclosed in Becker, that are not free-end specific. Applicant asserts that at the time the application was filed, the prior art failed to include any suggestion that a free-end specific antibody would be superior for treating Alzheimer's disease, compared to Becker's antibody that was specific for the β-sheet conformation of Aβ. Applicant again alleges that the examiner has not provided any rationale to suggest that at the time the application was filed one of ordinary skill in the art would have considered free end-specific antibodies to be superior to Becker's antibodies. Applicant asserts that the finding that free end-specific antibodies are superior to Becker's antibodies for treating Alzheimer's disease establishes that the claimed invention exhibits surprising and unexpected results compared to the closest prior art. Applicant asserts that such results are strong evidence that the claimed invention is not obvious over the prior art. Applicant alleges that the licensing of the claimed invention by erstwhile competitors and potential infringers is strong evidence that the claims are not obvious. Applicant alleges that the licenses granted under the subject application, even before it has issued as a patent, are additional strong, objective evidence that the claimed invention is not obvious.

Applicant's arguments have been fully considered and are not found persuasive. First applicant's alleged unexpected results are not commensurate in scope with the

claimed invention. While the clinical trials and licensing agreements concern two specific antibodies, bapineuzumab and PF-04360365, the claims are much more broadly drawn to methods of using antibodies that bind to the a free N-terminus or C-terminus of Aβ, including ones that bind to an epitope within residues 1-5 or residues 34-40. When an invention is predicated on an unexpected result, which typically involves synergism, an unpredictable phenomenon that highly dependent upon specific proportions and/or amounts of particular ingredients, any mixture of the components embraced by the claims which does not exhibit an unexpected result (e.g. synergism) is therefore *ipsto facto* unpatentable. Regardless, the results are not unexpected, as evidenced by the prior art of record. As set forth above, the teachings of Becker, Audia and Mak provide the expectation that 3D6 and antibodies to Aβ 34-40 would be effective in treating Alzheimer's disease.

Applicant's submitted evidence constitutes "secondary considerations." MPEP § 2145 states, "Evidence pertaining to secondary considerations must be taken into account whenever present; however, it does not necessarily control the obviousness conclusion. See, e.g., *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372, 82 USPQ2d 1321, 1339 (Fed. Cir. 2007) ("the record establish [ed] such a strong case of obviousness" that allegedly unexpectedly superior results were ultimately insufficient to overcome obviousness conclusion); *Leapfrog Enterprises Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1162, 82 USPQ2d 1687, 1692 (Fed. Cir. 2007)('given the strength of the *prima facie* obviousness showing, the evidence on secondary considerations was inadequate to overcome a final conclusion' of obviousness); and *Newell Cos., Inc. v.*

Kenney Mfg. Co., 864 F.2d 757, 768, 9 USPQ2d 1417, 1426 (Fed. Cir. 1988). Office personnel should not evaluate rebuttal evidence for its 'knockdown' value against the *prima facie* case, *Piasecki,* 745 F.2d at 1473, 223 USPQ at 788, or summarily dismiss it as not compelling or insufficient. If the evidence is deemed insufficient to rebut the *prima facie* case of obviousness, Office personnel should specifically set forth the facts and reasoning that justify this conclusion." Here too, because of the strength of the *prima facie* obviousness showing, the evidence of secondary considerations is inadequate to overcome a final conclusion of obviousness, as set forth above.

Conclusion

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

The examiner acknowledges applicant's comments set forth on the final page of the Remarks filed on 24 July 2009. Given that applicant has responded to six substantive office actions, the issues in the instant case have been well-developed on the record. Only three outstanding rejections under 35 U.S.C. 103(a) remain in this case. The examiner believes that this case may be in condition for appeal and decision by the Board of Patent Appeals and Interferences.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/G.E./

Gregory S. Emch
Patent Examiner
Art Unit 1649
05 November 2009

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
November 9, 2009